

AMENDMENTS

Claims 1-7, 9-12, and 14-20 are pending.

Claims 1, 4, and 11 have been amended.

Claims 14-20 have been added.

Support for the amendments is found in the claims and specification (e.g., page 10, for the concentration of the compound (A); page 11, for the compound (B); page 12, for the compound (D); and page 14, for the compound (C)), as originally filed. Support for claims 14 and 16 can be found on page 14, second paragraph. Claim 15 comprises the limitations of claim 1 and the third species of original claim 4 (see also page 6, paragraph (3)). Claims 17-20 comprise the limitations of original claims 3 and 5-7.

No new matter is believed to have been added.

Applicants wish to thank Examiner Roberts for discussions on March 18 and April 13, 2010. The undersigned Applicants' representative explained a difference between the claimed system and the disclosures of Chow et al. and Forward et al. Proposed experiments were discussed to address the obviousness rejection. The Examiner provided suggestions regarding the experiments and also indicated that in view of the proposed experiments the third species of the original claim 4 can be rejoined. Claim 15 is based on the Examiner's suggestion of rejoinder.

REMARKS/ARGUMENTS

The claimed invention provides for an oral preparation system which is able to form primary particles of calcium fluoride and to control the rate of calcium fluoride aggregation (namely, the formation of secondary particle) and accordingly allows for greater adsorption of calcium fluoride fine particles on teeth and is excellent in inhibiting demineralization and accelerating remineralization of teeth. See page 5 of the present specification.

In the claimed multi-composition oral system, (A) a calcium ion supplying compound and (B) a fluoride ion supplying compound, other than a monofluorophosphate ion supplying compound, are separated within the oral preparation system, and the monofluorophosphate ion supplying compound is present in either first (e.g., claim 1) or second (e.g., claim 15) composition.

Claims 1-3 and 5-13 are rejected under 35 U.S.C. 103(a) over Chow et al., US 5,891,448 and Forward et al., US 4,193,988. The rejection is traversed because the combination of the cited references does not describe or suggest the claimed oral system and the claimed system provides an advantageous result which would not have been expected from the combination of the cited references.

Chow et al. describe an oral system, wherein one composition of the system comprises a source of a calcium ion (col. 6, ln. 49-64) and the other composition comprises a source of a fluoride ion (col. 7, ln. 6-7). Abstract. An inhibitor of the formation of a calcium fluoride precipitate may be added to either one or both compositions of the system (col. 7, ln. 10-40) so that the formation of the calcium fluoride precipitate does not occur until at least 5 seconds after mixing (col. 4, ln. 54-60).

The goal of Chow et al. is to produce an initial delay in calcium fluoride formation and to control the rate of reactions that precipitate calcium fluoride (col. 4, ln. 45-50). Chow et al. describe that all conditions are carefully selected, e.g., the pH, the concentration of F ion is 3 mmols/L or greater, the concentration of Ca ion is 10 mmols/L or greater and the concentration of inhibitors is 100-1,000 higher than in the previous studies, etc. See col. 7, ln. 54-65. In comparison to the content of Ca, P, and F ions in remineralization systems, in the invention of Chow et al., the phosphate concentration, for the phosphate to act as an inhibitor, is low (e.g., 0.1 mmol/L) and should never reach the 1 mmol/L level. Col. 9-10, bridging paragraph. In contrast, in the remineralization systems, the level of Ca and P should be

comparable to each other to precipitate hydroxyapatite and the concentration of Ca and P is about 1-3 mol/L. Also, in the inventive system of Chow et al., only a small amount of P is present and a ratio of Ca/P is about 200. Col. 10, ln. 6-10.

Thus, Chow et al. distinguish their invention from remineralization systems. The present specification describes that the claimed composition accelerates remineralization and inhibits demineralization (page 9, ln. 11-13) and is therefore a remineralization system.

In addition, Chow et al. do not describe an oral system comprising a source of a monofluorophosphate ion (see Table 5 referred by the Examiner). The Examiner has relied on Forward et al. for this missing limitation.

Forward et al. describe an oral composition comprising sodium monofluorophosphate and glycerolphosphate for reducing solubility of dental enamel (abstract).

The Examiner has taken the position that adding monofluorophosphate to the first composition of Chow et al. would have been obvious because the activity of sodium monofluorophosphate in reducing the solubility of tooth enamel is enhanced by calcium glycerolphosphate (col. 1, ln. 22-26 of Forward et al.). See page 4 of the Official Action. Applicants respectfully disagree.

The Japanese patent application disclosed in paragraph [0008] of the present specification, JP-A No. Hei. 10-511956, is a family patent application of Chow et al. The problem associated with the Chow et al. system is described paragraph [0008]:

“Moreover, the composition containing calcium fluoride preformed in a colloidal form has also been proposed (Japanese Patent Laid-Open No. Hei 3-72415). However, it has a problem that the stability of the colloid decreases when preserving over a long period, and it thus fails to have an effect enough to deposit calcium fluoride particles on the tooth surface.”

Thus, Chow et al.’s system fails to have enough deposited calcium fluoride particles on the surface of a tooth.

Further, Forward describe that the acid resistance is increased (i.e., the solubility of tooth enamel is reduced) by the combination of monofluorophosphate and calcium glycerophosphate. No calcium fluoride, however, is formed by the combination of monofluorophosphate ion and calcium glycerophosphate only; and monofluorophosphate intake to the teeth (MFP-derived F in fluorine) is very small (see, e.g., D3, E3, and F3 in the table below).

Advantageous Effects of the Present Invention

The combination of (A), (B), (C) and (D) according to the present invention exerts an advantageous effect that would not have been obvious from the disclosures of Chow et al. and Forward et al. (a) in increasing monofluorophosphate intake to teeth surfaces and (b) in forming a uniform calcium fluoride coating with no space.

i) According to the claimed system, because of the presence of fluorine ion supplying compound (B), monofluorophosphate intake is remarkable increased as shown in the following Table. In Forward et al., which describe only a combination of monofluorophosphate and calcium glycerophosphate, and Chow et al., there is no disclosure regarding the means for doubling monofluorophosphate intake.

In the claimed system, by combining the fluorine ion supplying compound (B) with the combination of (A) and (C), and further with monofluorophosphate ion supplying compound (D), monofluorophosphate ions inhibit aggregation of calcium fluoride, thereby increasing not only the amount of calcium fluoride to be formed but also monofluorophosphate intake to teeth.

ii) Because of the presence of the monofluorophosphate ion supplying compound (D), the size of calcium fluoride particles is decreased, so that a calcium fluoride coating is formed without any space (see the SEM picture "S1" shown below; a clearer copy is attached with the submitted Declaration). In the composition containing no monofluorophosphate ions

similar to Chow et al., compared with the coating of the present invention, the size of calcium fluoride particles is larger and non-uniform, and areas in which no coating is formed are observed (see the SEM picture “S2” shown below; a clearer copy is attached with the submitted Declaration). Since the size of the calcium fluoride particles is large, the area that the calcium fluoride particles are in contact with a coating object (HAP pellet surface, that is, teeth surfaces) is small (i.e., the adhesion is low), so that a space is created between the coating object and calcium fluoride particles. The claimed system changes the quality and form of the coating of calcium fluoride by containing (D).

To take the SEM pictures shown below, S1 and S2, calcium lactate was used as the calcium ion supplying compound (A) because using calcium glycerophosphate leads to time-dependent changes that make photography difficult.

iii) By using the claimed system, monofluorophosphate ions are incorporated into calcium fluoride, and the fluorine intake is dramatically higher than that in Chow et al. (see the Table below and compare, e.g., inventive compositions D1, E1, and F1 to compositions D2, E2, and F2 similar to Chow et al. and composition D3, E3, and F3 similar to Forward et al., etc.). More specifically, the claimed system, which is not predictable based on Chow et al. and Forward et al., exerts an advantageous effect in increasing the quality and amount of calcium fluoride thus formed, and in increasing both of monofluorophosphate and fluorine intakes.

SEM Pictures

S1

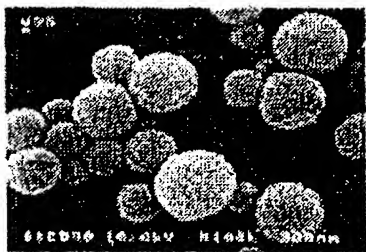


S1 corresponds to the claimed invention.

First composition: Sodium fluoride (50 mmol/l)

Second composition: Calcium lactate (50 mmol/l) and sodium monofluorophosphate (50 mmol/l)

S2



S2 does not correspond to the claimed invention.

First composition: Sodium fluoride (50 mmol/l)

Second composition: Calcium lactate (50 mmol/l)

The method for treating HAP in SEM pictures

HAP pellets (Apaceran APP-100, PENTAX) were each treated with the first composition and the second composition alternately three times for 30 seconds. The total treatment time for each pellet was 3 minutes.

The above SEM pictures show the surface condition of the treated HAP pellets.

Concerning F1 to F3, please consider the following points.

The content of fluorine is limited worldwide. The amount of fluorine which is allowed to be contained in one agent is limited to be 5,000 ppm or less. Since 210 $\mu\text{mol/g}$ is

about 4,000 ppm, in the case where the concentration of sodium monofluorophosphate and that of sodium fluoride in F1 are set to the upper limit of 210 $\mu\text{mol/g}$ each, the fluorine ion amount of F2 and that of F3 become 420 $\mu\text{mol/g}$ (=about 8,000 ppm) each. Such a fluorine ion concentration is an unrealistic concentration in formula (composition), so that the fluorine ion concentration of F2 and that of F3 are set to 210 $\mu\text{mol/g}$ each, while the concentration of sodium monofluorophosphate and that of sodium fluoride in F1 are set to 105 $\mu\text{mol/g}$ each.

Considering the preferable ratio of calcium ion to fluorine ion from the viewpoint of calcium fluoride formation, the calcium ion concentration is adjusted in F1 to F3, along with the adjustment of the fluorine ion amount mentioned above.

Applicants have conducted additional experiments showing the advantages of the claimed system which would not have been obvious based on the disclosure of the cited references. See also the Declaration submitted herewith.

Table

Unit ($\mu\text{mol/g}$)	D1	D2	D3	E1	E2	E3	F1	F2	F3	G1	H1
First Composition											
Calcium Glycerophosphate	50	50	50	1.25	1.25	1.25	200	200	200	200	1.25
Sodium Monofluorophosphate	25	—	50	2.6	—	5.2	105	—	210	—	—
Second Composition											
Sodium Fluoride	25	50	—	2.6	5.2	—	105	210	—	105	2.6
Sodium Monofluorophosphate	—	—	—	—	—	—	—	—	—	105	2.6
Treatment (*1)	Alter-nately	Alter-nately	Mixture	Alter-nately	Alter-nately	Mixture	Alter-nately	Alter-nately	Mixture	Alter-nately	Alter-nately
Fluorine Intake	2.0829	0.9466	0.0477	0.0167	0.0067	0.0046	4.0188	1.4584	0.0884	3.3372	0.0169
MFP-Derived (*2)	0.2818		0.0477	0.0009		0.0046	0.5437		0.0884	0.4515	0.0023
Calcium Fluoride Film	○	○	×	○	○	×	○	○	×	○	○

- (*1) Alternately: Immersed alternately in the first and second compositions for 30 seconds each (Immersed for a total of 3 minutes)
 Mixture: Immersed in the mixture of the first and second compositions for 3 minutes
- (*2) MFP: Sodium monofluorophosphate
- (*3) O: A calcium fluoride film is formed
- (*4) X: A calcium fluoride film is not formed
- The rest comprises purified water.

Method for Measuring Fluorine Intake

(1) A HAP pellet was treated alternately with the first composition of 10 ml and the second composition of 10 ml for 80 seconds each (total 3 minutes) or was treated with the mixture of the first composition and the second composition for 3 minutes. The treating method is the same as the method described in “b. Quantitative determination of amount of fluorine adsorption on HAP pellet” on pages 18-19 of the present specification.

(2) Comparative Examples were also conducted at a pH 7.

Method for Measuring MFP-Derived Fluorine Intake

The first mixture was mixed with the second mixture to form calcium fluoride particles. The calcium fluoride particles were separated and subjected to the measurement of a ratio of the number of moles of MFP to the number of moles of F by ion chromatography.

In D3, E3 and F3 each comprising only sodium monofluorophosphate as the component that contains fluorine, the amount of the fluorine intake was measured by determining the fluorine adsorption amount of the HAP pellet described in the present specification.

The fluorine intake amount was obtained by measuring the HAP pellet directly; however, the amount of the intake of MFP-derived fluorine was measured by ion chromatography of the calcium fluoride formed. Therefore, the measured value of MFP-derived fluorine intake compared to the measured value of fluorine intake may not be accurate; however, this data can be compared as a relative amount (the ratio of MFP-derived fluorine intake amount to fluorine intake amount). The method for measuring above-mentioned fluorine intake is different from the method for measuring above-mentioned MFP-derived fluorine intake.

As shown in the Table above, when the same amount of calcium ion is present, D1, E1 and F1 of the claimed system (each comprises MFP and sodium fluoride) show a higher

fluorine intake amount compared to that of D2, D3, E2, E3, F2 and F3 (each comprises MFP or sodium fluoride).

Moreover, when the amount of calcium is large (as in D1 and F1), it is clear that the amount of the MFP intake is significantly increased even though the MFP concentration is half of that of D3 and F3. From the results of D1, E1 and F1, the amount of the MFP intake is also increased when the calcium ion amount is 5 $\mu\text{mol/g}$ or more (see claims 14 and 16). When the MFP and calcium amounts are low (as in E1), the amount of the MFP intake is not always likely to be large. However, the fluorine intake (and the calcium fluoride film formation) is advantageous compared to the non-inventive systems of E2 and E3.

Claim 15. In G1, wherein the second composition comprises sodium fluoride and MFP, a significant increase in the amount of the fluorine intake and the MFP intake is noted, compared to F2 and F3 in which the calcium amount is the same and sodium fluoride or MFP is not used. In H1, wherein the second composition comprises sodium fluoride and MFP, an increase in the fluorine intake compared with E2 and E3 is shown.

It is also clear that F1, wherein sodium fluoride and MFP are separately contained in different compositions, is excellent in both of the fluorine intake and MFP intake, which is comparable with G1, wherein sodium fluoride and MFP are contained in the same composition.

As described above, it is clear from the data of the Table above that the use of sodium fluoride in combination with MFP increases the amount of fluorine adsorption. When the calcium amount is enough, monofluorophosphate ions promote aggregation of calcium fluoride so that the amount of monofluorophosphate intake is also increased.

Thus, the claimed oral preparation system provides an advantageous result which is not expected based on the disclosure of Chow et al. and Forward et al. Therefore, Chow et al.

and Forward et al. do not make the claimed system obvious. Applicants request that the rejection be withdrawn.

The objection of claim 13 is not applicable to the claims submitted herewith because claim 13 has been cancelled.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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